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Sequential intravenous/oral moxifloxacin versus intravenous piperacillin-tazobactam followed by oral amoxicillin-clavulanate for the treatment of complicated skin and skin structure infection☆

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Abstract

In this prospective, double-blind, multicentre trial, adult patients with complicated skin and skin structure infection (cSSSI) randomly received sequential intravenous (i.v.)/oral (p.o.) moxifloxacin (400 mg once a day) or a control regimen of i.v. piperacillin-tazobactam (3.0/0.375 g every 6 h) followed by p.o. amoxicillin-clavulanate (800 mg every 12 h), each for 7–14 days. Clinical cure rates at the test-of-cure visit (10–42 days post therapy) for the efficacy-valid population were 79% (143/180) for the moxifloxacin-treated group and 82% (153/187) for the control group (95% confidence interval, −12.04, 3.29). Bacteriological eradication rates for *Staphylococcus aureus*, the most prevalent organism, were 78% and 80%, respectively. The incidence of drug-related adverse events was similar for both groups (31% moxifloxacin, 30% control). Sequential i.v./p.o. moxifloxacin was as effective and well tolerated as i.v. piperacillin-tazobactam followed by p.o. amoxicillin-clavulanate in treating patients with cSSSI.

Keywords: Moxifloxacin; Piperacillin-tazobactam; Complicated skin and skin structure infections; Efficacy; Safety

1. Introduction

Complicated skin and skin structure infections (cSSSIs) are often the consequence of trauma or surgical procedures, especially in the setting of pre-existing neuropathy or vascular disease [1,2]. The clinical presentation of cSSSI is highly variable, ranging from infected ulcers to severe necrotizing fasciitis [1,2]. Skin and skin structure infections are categorised as complicated if there is a need for significant surgical intervention, when the infection involves deeper soft tissue, and when the infection is present in the setting of a complicating condition such as diabetes mellitus, arterial or venous insufficiency, or peripheral neuropathy that adversely affects the response to treatment [3]. Superficial infections or abscesses in anatomical areas where the risk of anaerobic or Gram-negative pathogen involvement is higher (e.g. rectal area) are also considered cSSSIs.

Excluding trauma-induced skin infections, *Staphylococcus aureus*, *Streptococcus pyogenes* (Group A β-haemolytic *Streptococcus*) and *Streptococcus agalactiae* (Group B β-haemolytic *Streptococcus*) are the pathogens most frequently isolated from immunocompetent patients with cSSSIs [4,5], although any bacteria, including those found on healthy skin, may cause infection. cSSSIs, which frequently occur in patients with underlying risk factors (e.g. vascular compromise, diabetes mellitus, other immunocompromised states), may be caused by difficult-to-treat or multiply-resistant Gram-positive and Gram-negative bacteria [3]. Anaerobic Gram-positive cocci and anaerobic Gram-negative bacilli

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are commonly isolated from some wounds (e.g. decubitus ulcers, diabetic foot ulcers, wounds associated with colorectal surgery, bite wounds).

Most cSSSIs are managed using empirical broad-spectrum antimicrobial therapy because of their polymicrobial nature (e.g. abscesses, diabetic foot infections, infected ischaemic ulcers, traumatic wound infections and bite wound infections).

Fluoroquinolones have characteristics that may explain their demonstrated efficacy in the treatment of cSSSIs. These characteristics include a broad spectrum of activity, rapid bactericidal action and adequate tissue concentrations at skin and deep tissue sites [6–11]. Specifically, moxifloxacin has broad-spectrum in vitro activity against common pathogens implicated in both uncomplicated and complicated skin and skin structure infections [12–16]. In addition to *S. aureus*, streptococci, Enterobacteriaceae and anaerobes (i.e. *Peptostreptococcus* spp., *Clostridium perfringens*, *Clostridium* spp. and *Bacteroides fragilis*), moxifloxacin also has in vitro activity against other pathogens isolated from patients with either animal or human bite infections (e.g. *Pasteurella multocida*, coagulase-negative *Staphylococcus* spp., *Prevotella* spp., *Fusobacterium* spp. and *Eikenella corrodens*) [17]. Because moxifloxacin has dual routes of excretion, no dosage adjustments are required in patients who exhibit renal impairment or need dialysis or who have mild to moderate hepatic insufficiency [18,19]. Dosage adjustments are also unnecessary when switching from intravenous (i.v.) to oral (p.o.) moxifloxacin, as the pharmacokinetic profile of each formulation is virtually interchangeable [20]. Moxifloxacin is not metabolised via the cytochrome P450 system, therefore it is not associated with drug interactions secondary to altered hepatic metabolism [20,21].

The objectives of the current trial were to evaluate the clinical and bacteriological efficacy and tolerability of sequential i.v./p.o. moxifloxacin compared with a control regimen of i.v. piperacillin-tazobactam followed by p.o. amoxicillin-clavulanate for the treatment of hospitalised patients with cSSSI. Although there are no standardised regimens for the management of cSSSI, the control regimen (piperacillin-tazobactam + amoxicillin-clavulanate) was selected because it is often used as an empirical regimen as it provides coverage against many β-lactamase-producing strains of *S. aureus* and difficult-to-treat Gram-negative bacteria [8].

2. Patients and methods

2.1. Study design and treatment

This study was a prospective, randomised, double-blind, double-dummy, multicentre Phase IIIb trial of adult patients with a diagnosis of cSSSI of <21 days duration (see entry criteria below). Routine aerobic and anaerobic cultures and susceptibility testing were performed prior to therapy. Patients were then randomised in a 1:1 ratio to receive moxifloxacin or the control regimen. Moxifloxacin recipients were administered 400 mg i.v. once a day for at least 3 days followed by oral moxifloxacin 400 mg once a day for a total duration of treatment of 7–14 days (Bayer Pharmaceuticals, West Haven, CT). Control patients received piperacillin-tazobactam 3.0/0.375 g administered i.v. every 6 h for at least 3 days followed by oral amoxicillin-clavulanate suspension 800 mg every 12 h for a total duration of treatment of 7–14 days. The decision to switch to oral therapy was made by the investigator, who was blinded to treatment, and was based upon the patient's clinical status and ability to tolerate oral therapy.

Written informed consent was obtained from each patient prior to receiving the first dose of study drug, and the institutional review board/ethics committee at each participating site approved the protocol.

2.2. Patient population

Hospitalised patients ≥18 years of age were eligible for enrolment if they had a cSSSI that was of known or suspected bacterial origin based on Gram stain and for whom at least 1 week of antibiotic therapy was anticipated. Specifically, patients with cSSSI included those with infected ischaemic ulcers, diabetic foot infections, infected decubitus ulcers, major abscesses, carbuncles, skin or skin structure infections requiring significant surgical intervention in addition to antimicrobial therapy, deep soft tissue infections (including surgical wound infections) and infections resulting from a human or animal bite. In addition, patients with cSSSIs in the presence of a complicating factor, which included pre-existing skin lesions or underlying conditions that adversely affect either the delivery of drug to the affected area, the immunological response or the tissue healing response (such as diabetes mellitus, vascular disease or peripheral neuropathy), were also eligible to participate in the study. Each patient also had at least three of the following signs and symptoms: drainage or discharge, erythema, fluctuance, heat or localised warmth, pain or tenderness, swelling or induration, fever (>37.5 °C axillary, >38 °C oral, >38.5 °C tympanic, or >39 °C rectal); or leukocytosis (absolute white blood cell count >12 000/mm^3); or >15% immature neutrophils (bands). Eligible patients also had appropriate specimens obtained for Gram stain and culture within 24 h prior to initiation of the study drug (i.e. by needle aspiration of purulent material or by biopsy).

Patients with any of the following diagnoses were excluded from the study: necrotizing fasciitis, Fournier's gangrene, ecthyma gangrenosum, streptococcal necrotizing fasciitis, streptococcal gangrene, clostridial necrotizing fasciitis or synergistic necrotizing fasciitis; folliculitis or furunculosis; diabetic foot infections or infected decubitus ulcers in the setting of suspected or documented osteomyelitis if the infected bone was not resected; secondary infections of a chronic skin disease (such as atopic dermatitis); infections

associated with prosthetic materials; infections where a surgical procedure alone was considered to be definitive therapy; diagnosis of an uncomplicated skin or skin structure infection; and infected burns. Also excluded were patients who were pregnant or nursing, and patients with any of the following medical conditions: immunological compromise including those receiving chronic immunosuppressive therapy (e.g. >15 mg/day of systemic prednisolone or equivalent); known hypersensitivity to the study drugs and β-lactam antibiotics; renal insufficiency (serum creatinine ≥2.5 mg/dL), or the need for haemodialysis or peritoneal dialysis; severe hepatic insufficiency (Child–Pugh class C); known congenital or sporadic syndromes of QTc prolongation or baseline QTc ≥500 ms; uncorrected hypokalaemia; seizure disorder; and history of fluoroquinolone-associated tendinopathy. Patients who had received prior antibiotic therapy, unless deemed a clinical failure with a persistent pathogen identified on culture at the time of enrolment, were also excluded from participation. Patients were also excluded if they had received prior antibiotics within 3 days of study enrolment for a dosing duration of >24 h or if they needed concomitant systemic antibiotic therapy for treatment of another infection.

2.3. Clinical and bacteriological assessments

Clinical signs and symptoms related to cSSSI were evaluated via serial clinical assessments prior to therapy, at the time of switch from i.v. to oral therapy or at days 3–5 during therapy, at the end of therapy, and at the test-of-cure visit (10–42 days post therapy). Clinical response at the test-of-cure visit (the primary efficacy variable) was defined as: cure (disappearance of acute signs and symptoms related to the infection or sufficient improvement such that additional antimicrobial therapy was not required); failure (insufficient resolution of the signs and symptoms of acute infection, requiring additional or alternative antimicrobial therapy); or indeterminate (assessment not possible for any reason). If a patient had more than one site of infection then the site with the worst response was used to rate the overall clinical response.

Cultures of infected skin tissue or structures were obtained by needle aspiration of obviously purulent material or by biopsy to avoid contamination with superficial colonising bacterial flora that may not have represented the causative pathogen. In addition, two sets of blood cultures were obtained prior to therapy and were repeated within 48 h if the pre-treatment cultures were found to be positive. The bacteriological response was based on the results of appropriate cultures taken before, during and after therapy. If more than one pathogen was isolated, each organism was assigned a bacteriological response. At the test-of-cure visit, a bacteriological response was categorised as: eradication (absence of the original pathogen(s) from a post-baseline blood and/or skin and skin structure culture specimen (confirmed eradication), or absence of post-baseline culture in a subject who had clinically responded to study therapy (presumed eradication)); persistence (presence of a baseline pathogen on a post-baseline blood and/or skin and skin structure culture specimen, or absence of appropriate culture material in a subject judged to be a clinical failure, or eradication of the original pathogen with a post-baseline positive culture with a new pathogen requiring treatment); or indeterminate (no possibility of determining the bacteriological response to treatment).

2.4. Safety and tolerability

Patients who received at least one dose of the study drug were monitored for adverse experiences. The safety of study drug therapy was evaluated by findings of physical examination, routine laboratory assessments (haematology, chemistry and urinalysis), electrocardiogram (ECG) monitoring and by the reporting of adverse events. The investigator categorised the intensity of each adverse event (mild, moderate or severe) and the relationship to the study drug (probable, possible, unlikely, none, or not assessable) prior to unblinding. Serious adverse events (i.e. those events that were fatal, life-threatening, required hospitalisation, resulted in disability, or otherwise endangered the patient) were recorded up to 21 days after the end of treatment.

2.5. Analysis populations

Three primary study populations were evaluated in the statistical analysis. The intent-to-treat (safety) population included all randomised patients who received at least one dose of study medication. The efficacy-valid population was defined as all patients who satisfied the following criteria: (1) met all entry criteria; (2) received no other concomitant systemic or topical antibacterial agents for ≥24 h with the study drug except narrow-spectrum agents for the treatment of isolated resistant organisms; (3) received study drugs for at least 2 days (if a clinical failure) or ≥5 days (if a clinical cure) with 100% compliance of study drug; and (4) had no protocol violations influencing the treatment efficacy. The microbiologically-valid population included all patients in the efficacy-valid population who had at least one causative organism identified at enrolment.

2.6. Statistical analyses

The primary objective of the study was to show that moxifloxacin was not inferior to the control regimen. The primary efficacy end point in this trial was the clinical response at the test-of-cure visit for the efficacy-valid population. Secondary efficacy end points included clinical response at other time points and in both the intent-to-treat and the microbiologically-valid populations. At each evaluation time point, two-sided 95% confidence intervals (CIs) were constructed around the mean clinical success and bacteriological eradication rate differences using cen-

tre size as Mantel–Hansel weights [22]. Non-inferiority was defined statistically as the lower limit of a two-sided 95% CI for the weighted difference (moxifloxacin–control) in clinical or bacteriological response rates being greater than −15%. A subgroup analysis was also performed to evaluate whether clinical response was influenced by infection type.

A logistic regression analysis was performed in the abscess patients to determine whether certain risk factors influenced the success rate in these patients. First, univariate analyses were performed, one at a time, for variables considered to be possible risk factors for clinical failure. A multiple logistic regression was then performed, including in the model only those variables with P-values <0.10 from the univariate analyses. Continuous independent variables were treated as continuous, with no collapsing done for the analysis.

Statistical summaries were provided for demographic and baseline characteristics. Categorical baseline demographic and medical variables were analysed using χ^2 tests. For continuous variables, a one-way analysis of variance (ANOVA) model was used to compare the two treatment groups.

Comparisons of the incidence rates of all types of adverse events were done in a descriptive manner. Events were tabulated by type (according to the MedDRA code) and by frequency for all events and for drug-related events. All adverse events occurring up to 7 days after the end of study drug therapy and all serious adverse events and deaths occurring up to 21 days after completion of study drug treatment were recorded. Laboratory data were analysed using descriptive statistics. For ECG data, mean changes from pre therapy were calculated for uncorrected QT, QTc, QRS and RR intervals by treatment.

3. Results

3.1. Patient disposition and baseline demographics and medical characteristics

A total of 617 patients were enrolled and randomised to study treatment from 12 December 2000 to 20 July 2003 from 59 investigational centres in the United States, Canada, Israel, Argentina, Chile and Peru. Sixteen patients did not receive study drug (eight per treatment group). Thus, 601 (97%) patients comprised the safety (intent-to-treat) population, of whom 367 patients comprised the efficacy-valid population (180 moxifloxacin, 187 control). Within the efficacy-valid population, 238 patients (119 in each treatment group) had at least one pre-therapy pathogen (microbiologically-valid population). Approximately 40% of enrolled patients (126 moxifloxacin, 124 control) were disqualified from the efficacy-valid population. The most common reasons for exclusion were use of prohibited pre-therapy, concomitant or post-therapy antibiotics (39 moxifloxacin, 41 control), insufficient treatment duration (18 moxifloxacin, 25 control), essential data missing (15 moxifloxacin, 13 control) and lost to follow-up (17 moxifloxacin, 11 control).

Table 1
Demographics and baseline medical characteristics of patients valid for efficacy analysis (efficacy-valid population)

Characteristic	Moxifloxacin (N = 180)	Control (N = 187)
Mean age ± SD, years (range)	52.4 ± 15.9 (18.0–89.0)	52.8 ± 15.4 (20.0–90.0)
Male gender, *n* (%)	118 (66)	122 (65)
Race, *n* (%)		
Caucasian	120 (67)	132 (71)
Black	30 (17)	30 (16)
Asian	1 (<1)	2 (1)
American Indian	1 (<1)	2 (1)
Hispanic	28 (16)	20 (11)
Uncoded	0 (0)	1 (<1)
Infection, *n* (%)		
Abscess	53 (29)	56 (30)
Cellulitis[a]	43 (24)	43 (23)
Diabetic foot infection	37 (21)	41 (22)
Infected ischaemic ulcer or decubitus ulcer	13 (7)	10 (5)
Surgical wound infection	12 (7)	8 (4)
Complicated erysipelas	0 (0)	2 (1)
Infection with traumatic lesion[b]	12 (7)	13 (7)
Other[c]	10 (6)	14 (7)

[a] Cellulitis includes cellulitis (n = 41), cellulitis with lymphoedema (n = 1) and cellulitis with venous stasis (n = 1).
[b] Infection with traumatic lesion includes infection of traumatic lesion, bite wound infection and infection with trauma.
[c] Other includes infected haematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, perirectal skin infection, infection of deep soft tissue and lymphangitis.

The overall demographic and baseline medical characteristics for the efficacy-valid population were comparable between the two treatment groups (Table 1). The study population comprised 65% males with a mean age of 52.6 years. Racial/ethnic composition was well balanced in both treatment groups except for a numerically greater percentage of Hispanic patients enrolled in the moxifloxacin (16%) versus the control group (11%; P = 0.17). The distribution of cSSSI types was similar between the two treatment groups, with abscess, cellulitis and diabetic foot infections reported most commonly (i.e. accounting for a total of ∼75% of all infections in each treatment group). Surgical procedures were performed in 55 (31%) moxifloxacin-treated and 63 (34%) control-treated patients. The most common surgical procedures were abscess drainage (32 (18%) moxifloxacin versus 37 (20%) control) and local debridement (20 (11%) in each treatment group).

For the efficacy-valid population, the majority of patients received i.v. followed by p.o. therapy: 85% (153/180) of the patients in the moxifloxacin group and 88% (165/187) in the control group. The mean duration of i.v. therapy was 6 days in both treatment groups.

3.2. Pre-therapy organisms and susceptibility profiles

The distribution of bacteria isolated from pre-therapy skin cultures in microbiologically-valid patients was generally similar between the two treatment groups. A total of 119 moxifloxacin-treated and 118 control patients had a pre-therapy isolate recovered from a skin and skin structure specimen. The most frequently isolated organism was *S. aureus* (54% moxifloxacin, 50% control) followed by non-group A β-haemolytic streptococci (*S. agalactiae* and *Streptococcus dysgalactiae*) (16% moxifloxacin, 27% control), *Enterococcus faecalis* (15% moxifloxacin, 10% control), *S. pyogenes* (15% moxifloxacin, 10% control), *Peptostreptococcus* spp. (8% moxifloxacin, 10% control) and *Escherichia coli* (7% moxifloxacin, 10% control). A total of 10 (8%) patients treated with moxifloxacin had methicillin-resistant *S. aureus* (MRSA) isolates compared with 7 (6%) treated with control agents. *Pseudomonas aeruginosa* was isolated from 5 (4%) moxifloxacin-treated and 11 (9%) control-treated patients. Overall, patients with a monomicrobial infection (50% moxifloxacin, 55% control) were most often infected with *S. aureus*. Polymicrobial infections occurred in 50% (60/119) of moxifloxacin-treated versus 45% (53/118) of control-treated patients. The majority of pre-therapy Enterobacteriaceae and anaerobes were cultured from polymicrobial infections. Furthermore, infections in patients with abscesses, diabetic foot infections, cellulitis and surgical wound infections tended to be polymicrobial and had the greatest number of pathogens.

Seven moxifloxacin-treated patients had bacteraemia and the organisms isolated were (*N*): *S. aureus* (2), *S. pyogenes* (2), *S. agalactiae* (1), *E. faecalis* (2) and *P. aeruginosa* (1). Three control-treated patients also had bacteraemia and the organisms were (*N*): *S. aureus* (1), *S. pyogenes* (1) and *S. agalactiae* (1).

The susceptibility profiles of all pre-therapy isolates to moxifloxacin demonstrated excellent in vitro activity, with MIC_{90} values (minimum inhibitory concentration that inhibits the growth of 90% of a bacterial strain) for *S. aureus*, *S. pyogenes*, *S. agalactiae*, *E. coli*, *Proteus mirabilis*, *Enterobacter cloacae* and *Klebsiella pneumoniae* ≤1.0 mg/L. MIC_{90} values were higher for certain bacteria, such as *E. faecalis* (>32 mg/L), *Peptostreptococcus* spp. (1.0 mg/L), *Prevotella* spp. (2.0 mg/L) and *Bacteroides* spp. (>32 mg/L). There was no evidence of an emergence of in vitro resistance during treatment, as demonstrated by the comparison of MIC values before and during/post treatment (data not shown).

Against *S. aureus*, the most commonly isolated organism, the mean MIC_{90} value was 4.0 mg/L for both piperacillin-tazobactam and amoxicillin-clavulanic acid. Mean MIC_{90} values of piperacillin-tazobactam were ≤0.5 mg/L for *S. pyogenes*, *S. agalactiae* and *P. mirabilis* and ≤4.0 mg/L for *E. coli*, *E. cloacae*, *K. pneumoniae* and *P. aeruginosa*. Mean MIC_{90} values of amoxicillin-clavulanic acid were ≤0.12 mg/L for *S. pyogenes* and *S. agalactiae* and ≤4.0 mg/L for *E. coli* and *K. pneumoniae*.

Table 2
Clinical cure at test-of-cure visit by infection type for efficacy-valid population

Diagnosis	Moxifloxacin *n*/*N* (%)	Control *n*/*N* (%)
Overall	143/180 (79)	153/187 (82)
By infection type:		
Abscess	42/53 (79)	52/56 (93)
Cellulitis	36/43 (84)	38/43 (88)
Diabetic foot infection	25/37 (68)	25/41 (61)
Infected ischaemic ulcer or decubitus ulcer	10/13 (77)	6/10 (60)
Surgical wound infection	11/12 (92)	8/8 (100)
Complicated erysipelas	–	2/2 (100)
Infection with traumatic lesion	11/12 (92)	10/13 (77)
Other infection types[a]	8/10 (80)	12/14 (86)

[a] Other includes infected haematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, perirectal skin infection, infection of deep soft tissue and lymphangitis.

3.3. Clinical and bacteriological outcomes

For the efficacy-valid population, overall clinical cure rates at the test-of-cure visit were 79% for moxifloxacin-treated versus 82% for the control group, supporting that moxifloxacin was not inferior to the control regimen (95% CI, −12.04%, 3.29%).

The clinical cure rates for the efficacy-valid population were generally comparable between the treatment groups when stratified by infection type (Table 2). One exception was that patients with abscess had a higher response rate following piperacillin-tazobactam (93%) compared with the moxifloxacin group (79%) ($P = 0.04$). As there were more patients with abscess in the moxifloxacin group with polymicrobial infections (22/53 (42%) in the moxifloxacin group versus 15/56 (27%) in the control group), positive baseline MRSA cultures (7/53 (13%) versus 1/56 (2%)), serum albumin levels below 3 g/dL (18/53 (34%) versus 10/56 (18%)), positive baseline *Prevotella* spp. cultures (9/53 (17%) versus 3/56 (5%)) and a delayed first surgical procedure (11/53 (21%) versus 5/56 (9%)), a univariate logistic regression analysis was performed for patients with abscesses to identify the risk factors that were associated with treatment failure. Four risk factors were identified that appeared to be associated with treatment failure (Table 3): number of surgeries ($P < 0.001$), treatment with moxifloxacin ($P = 0.05$), resistance to piperacillin-tazobactam ($P = 0.05$) and presence of MRSA ($P = 0.06$). A subsequent multiple logistic regression model using number of surgeries, treatment group and presence of MRSA as predictors found that the only significant predictor was the number of surgeries, with patients undergoing two or more procedures being at increased risk of failure ($P = 0.04$; odds ratio (OR) = 2.90 (95% CI, 1.05, 8.04)). There was no significant difference between treatment groups after adjusting for the number of surgeries, resistance to piperacillin-tazobactam and the presence of MRSA

Table 3
Association of selected variables with clinical failure for patients with abscess: a univariate regression model

Variable	*P*-value
Treatment group	0.05
Sex	0.71
Age	0.96
Duration of infection	0.56
Day of first surgery	0.86
Number of surgeries	<0.001
Albumin	0.78
Number of co-morbid conditions	0.60
Congestive heart failure	0.52
Diabetes mellitus	0.66
Predisposing conditions	0.97
Cancer	0.99
Renal disease	0.19
Lymphoedema	0.99
Body mass index	0.70
Number of organisms isolated	0.72
MRSA	0.06
Resistance to piperacillin-tazobactam	0.05
Resistance to amoxicillin-clavulanate	0.21
Prevotella spp.	0.76

MRSA, methicillin-resistant *Staphylococcus aureus*.

($P = 0.12$; OR = 1.05 (95% CI, 0.99, 1.12)). Similarly, presence of MRSA ($P = 0.70$; OR = 1.86 (95% CI, 0.01, 50.00)) or resistance to piperacillin-tazobactam did not predict failure after adjusting for the other variables ($P = 0.25$; OR = 4.83 (95% CI, 0.34, 68.86)).

In contrast, patients with infected ischaemic ulcer or decubitus ulcer and infections associated with a traumatic lesion had a somewhat higher response rate following moxifloxacin than control therapy (Table 2). However, the significance of these differences is not known because the number of patients with these diagnoses is small in both treatment groups. In addition, although the response rate was higher for patients with diabetic foot infections treated with moxifloxacin, this was not statistically significant ($P = 0.54$).

Bacteriological eradication rates at the test-of-cure visit for the microbiologically-valid population were similar in the two treatment groups for most pathogens (Table 4). For methicillin-sensitive *S. aureus* strains, the most frequently isolated organism, bacteriological eradication was 81% in each treatment group. Eradication of MRSA was lower in both treatment groups (60% (6/10) moxifloxacin, 71% (5/7) control). Bacteriological eradication rates for patients with polymicrobial infection were lower than those for monomicrobial infection both in the moxifloxacin group and the control group. Eradication rates for monomicrobial infections were 85% in both treatment groups and for polymicrobial infections they were 70% in the moxifloxacin-treated group versus 77% in the control-treated group.

For patients with abscess, there was a difference in the frequency of *S. aureus* infections and eradication rates between the two treatment groups. The bacteriological eradication rate for *S. aureus* was 78% (21/27) for moxifloxacin-treated patients compared with 88% (15/17) for control-treated

Table 4
Clinical cure and bacteriological eradication rates at the test-of-cure visit for efficacy-valid patients with selected causative pre-therapy skin organisms (microbiologically-valid population)

Organism	Moxifloxacin *n*/*N* (%)		Control *n*/*N* (%)	
	Clinical cure	Bacteriological eradication[a]	Clinical cure	Bacteriological eradication[a]
Gram-positive aerobes				
Staphylococcus aureus	50/64 (78)	50/64 (78)	47/59 (80)	47/59 (80)
Streptococcus pyogenes	13/18 (72)	13/18 (72)	8/12 (67)	8/12 (67)
Streptococcus agalactiae	7/13 (54)	7/13 (54)	19/25 (76)	20/25 (80)
Enterococcus faecalis	12/18 (67)	12/18 (67)	9/12 (75)	9/12 (75)
Gram-negative aerobes				
Enterobacteriaceae				
Escherichia coli	7/8 (88)	7/8 (88)	11/12 (92)	11/12 (92)
Klebsiella pneumoniae	5/6 (83)	5/6 (83)	4/7 (57)	4/7 (57)
Proteus mirabilis	3/5 (60)	3/5 (60)	5/6 (83)	5/6 (83)
Enterobacter cloacae	4/5 (80)	4/5 (80)	1/2 (50)	1/2 (50)
Gram-positive anaerobes				
Peptostreptococcus spp.[b]	6/10 (60)	6/10 (60)	11/12 (92)	11/12 (92)
Gram-negative anaerobes				
Bacteroides spp.[c]	9/9 (100)	9/9 (100)	9/10 (90)	9/10 (90)
Prevotella spp.[d]	9/14 (64)	9/14 (64)	9/11 (82)	9/11 (82)
Monomicrobial infection	50/59 (85)	50/59 (85)	55/65 (85)	55/65 (85)
Polymicrobial infection	42/60 (70)	42/60 (70)	41/53 (77)	41/53 (77)

[a] Includes confirmed eradication and presumed eradication.
[b] Includes *Peptostreptococcus* spp., *P. anaerobius*, *P. asaccharolyticus*, *P. magnus*, *P. prevotii*, *P. tetradius* and *P. micros*.
[c] Includes *Bacteroides* spp., *B. fragilis*, *B. merdae*, *B. stercoris*, *B. thetaiotaomicron* and *B. uniformis*.
[d] Includes *Prevotella* spp., *P. buccae*, *P. oris*, *P. bivia*, *P. disiens*, *P. melaninogenica*, *P. oralis*, *P. intermedia*, *P. tannerae* and *P. veroralis*.

patients. Of the 44 moxifloxacin-treated abscess patients with skin isolates, 7 had MRSA in contrast to only 1 control-treated patient with MRSA. Excluding the MRSA isolates in patients with abscess, the bacteriological eradication rates were similar between the two treatment groups (85% moxifloxacin, 88% control). For patients with diabetic foot infections, *S. aureus* was the most common pathogen isolated from both treatment groups. Moxifloxacin had higher eradication rates against *S. aureus* (81% (13/16)) compared with the control group (67% (12/18)).

Clinical and bacteriological response rates were highly correlated within the two treatment groups for most pathogens (Table 4).

3.4. Safety and tolerability

Table 5 provides an overview of adverse events, serious adverse events, premature discontinuations due to adverse events, and drug-related adverse events. In general, the two treatment groups were comparable based on investigator-reported adverse event rates. The incidence of any adverse event (regardless of relatedness to the study drug) was 75% (223/298) for the moxifloxacin-treated group and 72% (218/303) for control-treated patients. The majority of adverse events were of mild or moderate intensity (≥90%). Rates of early withdrawal of study drug owing to an adverse event also were comparable (9% moxifloxacin, 10% control). Premature discontinuation of study drug due to an adverse event was reported for 27 moxifloxacin-treated patients (14 were drug related) and 31 control-treated patients (17 were drug related). The most common reasons for early withdrawal of therapy included cellulitis (3 moxifloxacin versus 4 control), hypersensitivity (2 moxifloxacin versus 3 control), osteomyelitis (4 moxifloxacin versus 1 control), rash (3 moxifloxacin versus 2 control), impaired healing (no moxifloxacin versus 4 control) and skin ulcer (2 moxifloxacin versus 1 control).

Serious adverse events occurred at similar rates between the moxifloxacin (41/298 (14%)) and control groups (44/303 (15%)). The most common serious adverse events included cellulitis (3 moxifloxacin versus 6 control), osteomyelitis (3 moxifloxacin versus 6 control) and localised infection (4 moxifloxacin versus 2 control). Five serious events in the moxifloxacin group and 10 serious events in the control group were judged by the investigator to be drug related. In the moxifloxacin group, probable or possible serious drug-related adverse events included weakness, worsening of drug reaction rash, exacerbation of cellulitis, pseudomembranous colitis and clinical failure. Corresponding serious drug-related adverse events in the control group included cardiopulmonary arrest, worsening congestive heart failure, allergic reaction, asthenia, worsened skin eruption, allergic reaction, persistent abscess of the right leg, bloody diarrhoea, osteomyelitis and clinical failure. Only 6 patients died during the study surveillance period (3 in each treatment group); none of these deaths were assessed as related to the treatment of cSSSI.

The proportion of patients with a drug-related adverse event at the test-of-cure visit was 31% (93/298) for moxifloxacin versus 30% (91/303) for the control group (Table 5). The only two drug-related adverse events that occurred in ≥3% of patients were diarrhoea (5% moxifloxacin, 8% control) and nausea (4% moxifloxacin, 2% control).

Table 5
Overview of adverse events

Adverse event	Moxifloxacin ($N = 298$) n (%)	Control ($N = 303$) n (%)
Any treatment-emergent adverse event	223 (75)	218 (72)
Serious adverse event	41 (14)	44 (15)
Premature discontinuation due to adverse event	27 (9)	31 (10)
Any drug-related adverse event	93 (31)	91 (30)
Diarrhoea	16 (5)	25 (8)
Nausea	11 (4)	7 (2)

4. Discussion

This randomised, double-blind, controlled study demonstrated that a once daily regimen of moxifloxacin was well tolerated and as effective as a regimen requiring multiple daily doses of i.v. piperacillin-tazobactam followed by p.o. amoxicillin-clavulanate for the treatment of patients with cSSSI. Clinical cure rates by infection type showed comparable cure rates for i.v./p.o. moxifloxacin compared with i.v. piperacillin-tazobactam followed by p.o. amoxicillin-clavulanate for the most common skin infections encountered. Moxifloxacin monotherapy was effective at eradicating the most common Gram-positive and Gram-negative aerobic and anaerobic bacteria implicated in cSSSIs.

Findings of this trial are consistent with earlier reports that found that moxifloxacin is effective for the treatment of uncomplicated skin and skin structure infections [23–25]. In one study, 90% and 91% of moxifloxacin- and cephalexin-treated patients, respectively, were clinical cures [23]. In addition, the moxifloxacin and cephalexin regimens eradicated the most frequently isolated pathogen, *S. aureus*, in 92% and 93% of the evaluable infections, respectively.

Initial treatment for cSSSI requires empirical therapy with a broad-spectrum antimicrobial agent along with appropriate surgical intervention. Antimicrobial treatment of patients with cSSSI can include a penicillinase-resistant penicillin, penicillin/β-lactamase inhibitor combination, cephalosporin or fluoroquinolone [8,26–29]. Vancomycin is recommended for suspected or documented infections due to methicillin-resistant *Staphylococcus* spp. or in cases of allergy to β-lactam antibiotics. Once results from appropriate culture and susceptibility tests become available, appropriate therapy should be continued. Effective empirical therapy can require multiple daily doses of one or more antibiotics. Sequential

i.v./p.o. moxifloxacin is dosed once daily. In addition, no dosage adjustment is required for moxifloxacin when patients are switched from i.v. to oral therapy [20].

In this study, the most frequent causative bacteria isolated at baseline were consistent with those expected for cSSSIs [4,5], and approximately one-half of evaluable patients had a polymicrobial infection. Moxifloxacin was effective against a wide variety of bacteria isolated from the study patients. The eradication rate for patients with *S. aureus*, the most frequently isolated organism, was 78% in the moxifloxacin group and 80% in the piperacillin-tazobactam/amoxicillin-clavulanate group. As expected, the eradication rate of MRSA was lower in both treatment groups (60% in the moxifloxacin and 71% in the control group). Eradication rates were similar between the two treatment groups against other frequently encountered pathogens (e.g. *S. pyogenes*, *E. coli*, *Bacteroides* spp.).

Patients in both treatment groups with polymicrobial infections tended to have higher rates of persistence or presumed persistence and lower cure rates compared with monomicrobial infections. These results are consistent with animal models that have demonstrated that polymicrobial infections can be more pathogenic than monomicrobial infections [30].

Diabetic foot infections are often difficult to treat because the patient typically has peripheral vascular disease with subsequent poor blood flow, potentially compromising adequate tissue penetration of many antibiotic regimens [31]. In this study, patients with diabetic foot infection tended to have slightly higher clinical cure rates after moxifloxacin therapy (68%) versus the control regimen (61%), although this difference did not reach statistical significance. Classification of diabetic foot infection in this study was made by the treating investigator. Given the variability in definitions of diabetic foot infection, additional subanalyses were performed to determine whether potential differences in how investigators defined diabetic foot infections could in part explain the observed response rates. The definitions used were: (1) diabetic patient with any infection of the foot or leg; (2) diabetic patient with any infection of the foot or leg and an associated ulcer; and (3) diabetic foot infection as classified by the investigator and an associated ulcer. With all three definitions, response rates were consistently better for patients in the moxifloxacin group than for those in the control group (data not shown).

We observed a lower response in moxifloxacin-treated patients who presented with abscess. There were multiple imbalances between the treatment groups that could have potentially contributed to the observed differences in response, including more patients in the moxifloxacin group having polymicrobial infections, MRSA infection and delays in the first surgical procedure. However, multiple regression analysis identified the number of surgeries as being the only independent predictor of treatment outcome, with patients undergoing two or more procedures being at increased risk of failure ($P = 0.04$). These results are somewhat unexpected in that for other types of abscesses, such as liver and pancreatic abscesses, polymicrobial infections are associated with worse clinical outcomes [32–35]. In addition, moxifloxacin and the comparator regimen used in this study are not indicated for the treatment of infections caused by MRSA. Thus, these agents would be expected to be less efficacious against this pathogen. Finally, although effective treatment of abscesses requires timely surgical drainage [36], the delays noted in this study may also have occurred in patients with less severe infections for whom surgery could be delayed without affecting clinical outcome.

This study also demonstrated that moxifloxacin and the control regimen had excellent safety and tolerability profiles. The rates of drug-related events, serious adverse events and deaths were similar for both treatments. Overall, the adverse event patterns were similar for moxifloxacin and piperacillin-tazobactam followed by amoxicillin-clavulanate. Diarrhoea and nausea were the two most commonly reported drug-related adverse events in both treatment groups.

In conclusion, sequential i.v./p.o. moxifloxacin monotherapy was found to be safe and as effective as i.v. piperacillin-tazobactam followed by p.o. amoxicillin-clavulanate therapy for the treatment of cSSSI. Accordingly, moxifloxacin can be considered a reasonable option for the treatment of cSSSI because of its once daily dosing, safety profile, available oral formulation and broad-spectrum antimicrobial activity.

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